Claim 17 (new): The betacellulin mutein or a salt thereof according to claim 1, wherein the mutein has the pancreatic β cell differentiation promoting activity and the reduced epithelial cell growth promoting activity.

REMARKS

Claims 1-16 were pending in the application. Claims 14 and 16 have been cancelled without prejudice as being drawn to a non-elected invention. Claims 3-11 have also been cancelled without prejudice. Claim 1 has been amended to incorporate a limitation of dependent claim 7. Claim 2 has been amended to correct a typographical error. Claim 15 has also been amended. New claim 17 has been added. Support for new claim 17, as well as the amendments to claims 1, 2, and 15, can be found in the claims and the specification as originally filed. After entry of the instant amendment, claims 1, 2, 12, 13, 15, and 17 will be pending. The specification has been amended to add sequence identifiers. Applicants note that all references to page/line numbers in the amendments to the specification refer to the page/line numbers of the application as originally filed. No new matter has been added by way of the new claim or the amendments to the specification or the claims. Applicants reserve the right to pursue the subject matter of the cancelled claims in this or a separate application.

Sequence Rules

The application has been objected to because the specification is not in compliance with 37 C.F.R. §§1.821-1.825 of the Sequence Rules and Regulations. Specifically, the Examiner has objected to the lack of sequence identifiers (SEQ ID NOs) for the sequences in Figure 10 and on page 11 (lines 7-12). Applicants have amended the specfication to add the required sequence idenfiers and respectfully submit that the specification is in compliance with 37 C.F.R. §§1.821-1.825.

Objection to Claims 2, 5-7, 10, and 11

Claim 2 was objected to because of the spelling of "ratioof". Applicants have amended claim 2 to replace "ratioof" with "ratio of", obviating the objection to this claim.

Claims 5-7, 10, and 11 have been objected to because they are directed to non-elected inventions. Claims 5-7, 10, and 11 have been cancelled without prejudice, obviating the objection of these claims.

Rejection of Claims 1-13 and 15 Under 35 U.S.C. §112, First Paragraph

Claims 1-13 and 15 have been rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, according to the Examiner,

> the specification fails to teach how to make a betacellulin mutein (SEQ ID NO:38) wherein the β cell differentiation promoting activity is preserved and the epithelial growth promoting activity is reduced and wherein the ratio of the pancreatic β cell differentiation promoting activity to the epithelial cell growth promoting activity is at least twice relative to that of betacellulin. The results of BTC24-76 (SEQ ID NO:38) presented in Table 14 do not concur with the limitations of the claims.

Applicants respectfully traverse this rejection. Table 14 presents the results of the measurement of the β cell differentiation promoting (BTC) activity and the epithelial cell growth promoting (EGF) activity of various betacellulin muteins and betacellulin. The results are presented as EC50 and IC50 values, respectively. An increase in these values corresponds to a decrease in BTC and/or EGF activity. That is, the relative activities can be represented as the reciprocal of the values shown in Table 14 as follows:

	BTC activity	EGF activity
Met-BTC80	1/0.07 = **14.29**	1/1.2 = **0.83**
Met-BTC76	1/0.30 = **3.33**	1/95.1 = **0.011**
BTC2-76	1/0.12 = **8.33**	1/38.6 = **0.026**
BTC24-76	1/0.03 = **33.33**	1/11.0 = **0.091**

As shown above, the BTC activity of BTC24-76 (SEQ ID NO:38) is preserved as compared to the control (compare 33.33 to 14.29), and the EGF activity is reduced (compare 0.091 to 0.83), as required by claim 1. Claim 2 requires that the ratio of the BTC activity to the EGF activity is at least twice relative to that of betacellulin. Using the values calculated above, the following table shows the BTC/EGF activity ratio:

	BTC/EGF activity ratio
Met-BTC80	14.29 / 0.83 = **17.22**
Met-BTC76	3.33 / 0.011 = **302.7**
BTC2-76	8.33 / 0.026 = **320.4**
BTC24-76	33.33 / 0.091 = **366.3**

As shown above, the ratio of the BTC activity to the EGF activity for BTC24-76 (SEQ ID NO:28) is at least twice that of betacellulin (compare 366.3 to 17.22). Accordingly, Applicants

submit that the data presented in Table 14 of the specification clearly teaches the limitations of claims 1 and 2, contrary to the assertions of the Examiner.

The Examiner further states that "the specification fails to teach how to use BTC24-76 in a method for the prophylaxis or treatment for diabetes in mammals." Accordingly, it is the Examiner's position that "undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope." Applicants respectfully traverse this rejection.

Claim 15 has been amended such that it is no longer directed to a "prophylaxis". Accordingly, the rejection based on the recitation of "prophylaxis" is rendered moot. As amended, claim 15 is directed to a method for treatment for diabetes, characterized in that a betacellulin mutein or salt thereof according to claim 1 is administered to mammals. As amended, claim 15 is enabled.

A patent application need not teach, and preferably omits, what is well known in the art (see M.P.E.P. § 2164.01). Furthermore, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation (see M.P.E.P. § 2164.01(c)). Methods of administering drugs to treat diabetes were well-known in the art at the time the instant application was filed. Furthermore, methods of treating diabetes in mice using full-length betacellulin were also known (see Appendix A, attached herewith). Given that the betacellulin muteins of Applicants' invention are an improvement over full-length betecellulin, one of skill in the art would have an expectation of success in the use of said muteins in the treatment of diabetes. Accordingly, it would not require undue experimentation for one of skill in the art practice the instant invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Rejection of Claims 3-11 Under 35 U.S.C. §112, Second Paragraph

Claims 3-11 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite "for failing to particularly point out and distinctly claim the subjected matter which applicant regards as the invetion." In order to expedite prosecution, and in no way conceding to the validity of the rejection, Applicants have cancelled claims 3-11 without prejudice. Accordingly, Applicants respectfully submit that the rejection of these claims under 35 U.S.C. §112, second paragraph is rendered moot.

Rejection of Claims 1, 3, and 7 Under 35 U.S.C. §102(e)

Claims 1, 3, and 7 were rejected under 35 U.S.C. §102(e) as being anticipated by Wei et al., U.S. Patent No. 6,410,506 B1. The Examiner relies on Wei et al. as teaching "an amino acid sequence comprising the sequence represented by SEQ ID NO:38." Specifically, the Examiner relies on SEQ ID NO:13 of Wei et al. as anticipating the instant claims. Applicants respectfully traverse this rejection.

Applicants submit that the cancellation of claims 3 and 7 renders the rejection of these claims moot.

As amended, claim 1 is directed to a betacellulin mutein or a salt thereof comprising the amino acid sequence represented by SEQ ID NO: 38, wherein the pancreatic β cell differentiation promoting activity is preserved, and the epithelial cell growth promoting activity is reduced.

In order to anticipate a claim, a prior art reference must disclose each an every element of that claim. The sequence disclosed by Wei at al. is a 177 amino acid polypeptide. Wei at al. does not specifically disclose the isolated 53 amino acid peptide of SEQ ID NO:38, or specify the desirability of using a peptide comprising this specific sequence. Furthermore, Wei at al. does not disclose a polypeptide of SEQ ID NO:38, wherein the pancreatic β cell differentiation promoting activity is preserved, and the epithelial cell growth promoting activity is reduced.

Accordingly, Applicants submit that Wei et al. does not anticipate claim 1, as amended, or any claims dependent therefrom. Applicants further submit that new claim 17 is not anticipated by Wei at al.

In view of the forgoing, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §102(e).

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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